Post Transplant Viral Infections

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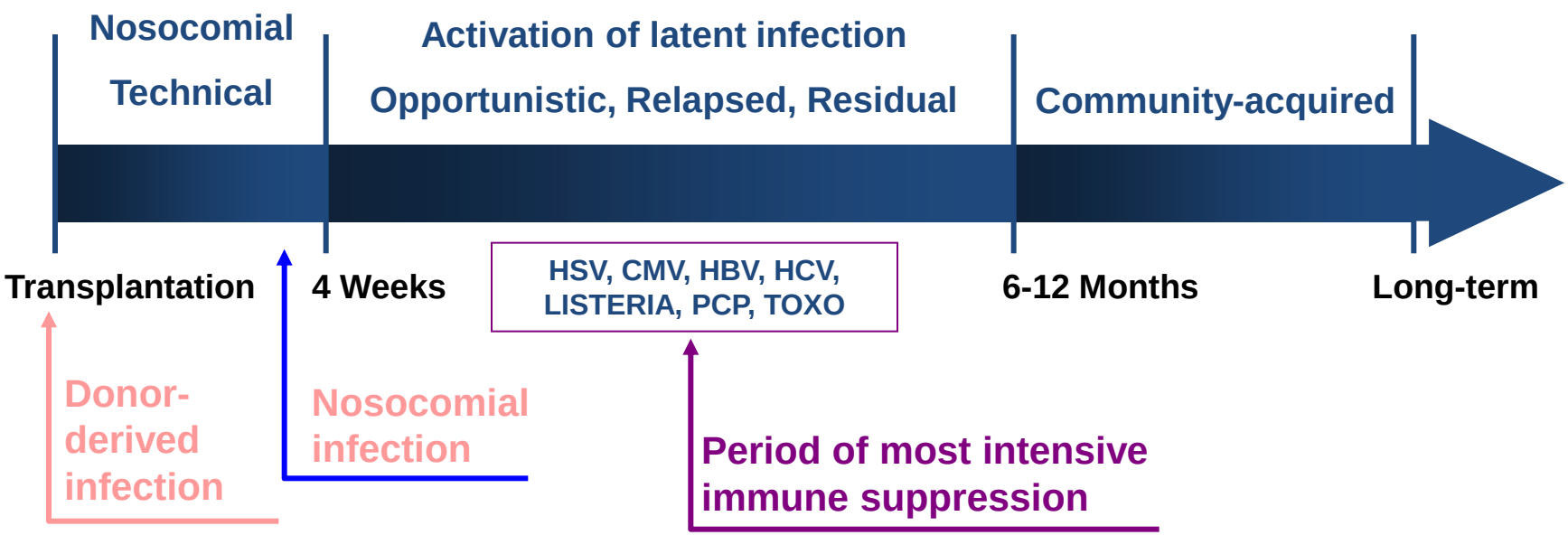
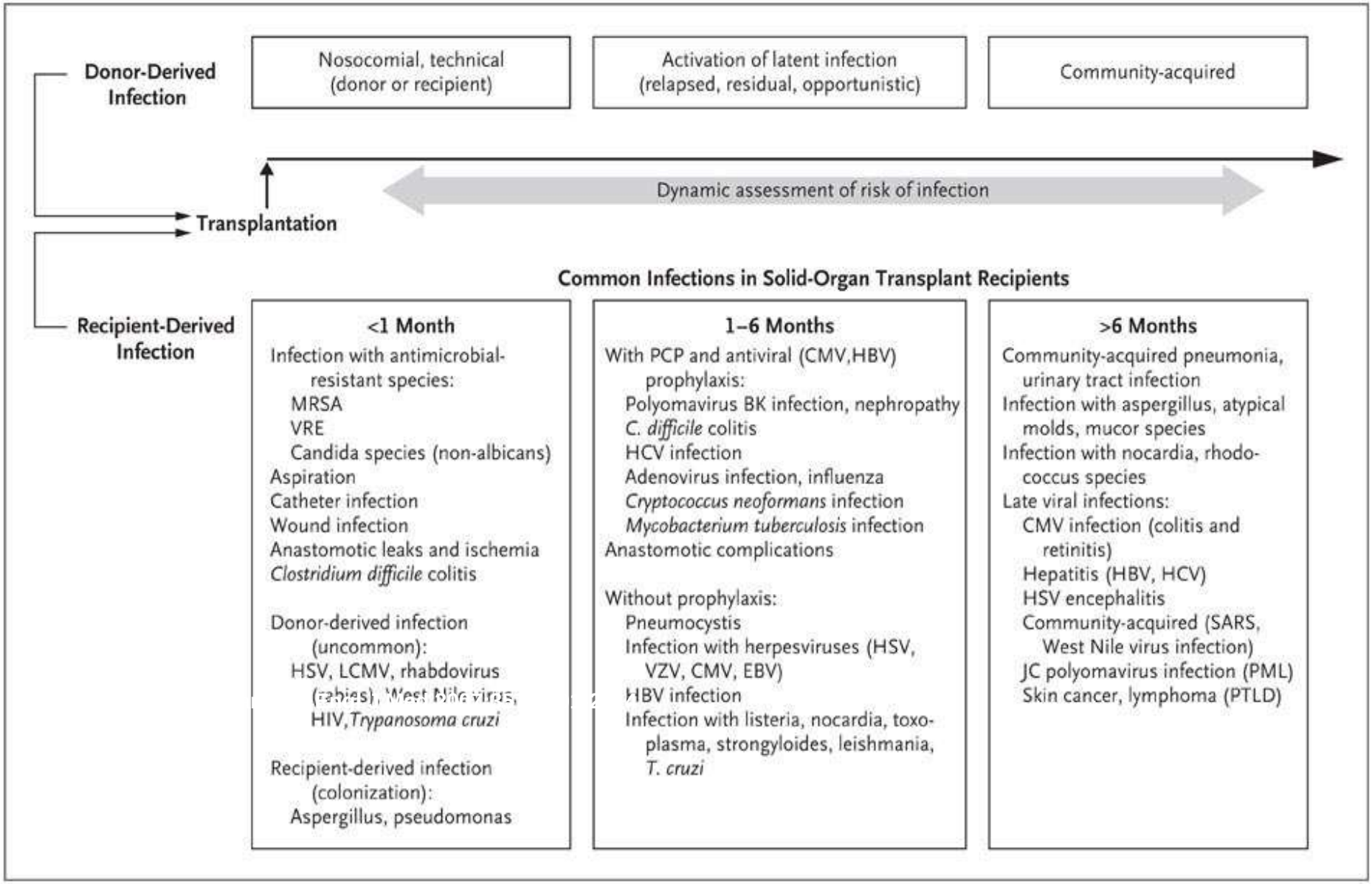
Timeline of Post transplant Infections



Common Variables in Immune Suppression

- Rejection, antirejection therapy, new agents
- Neutropenia, lymphopenia
- Viral coinfection (CMV, HCV, EBV)

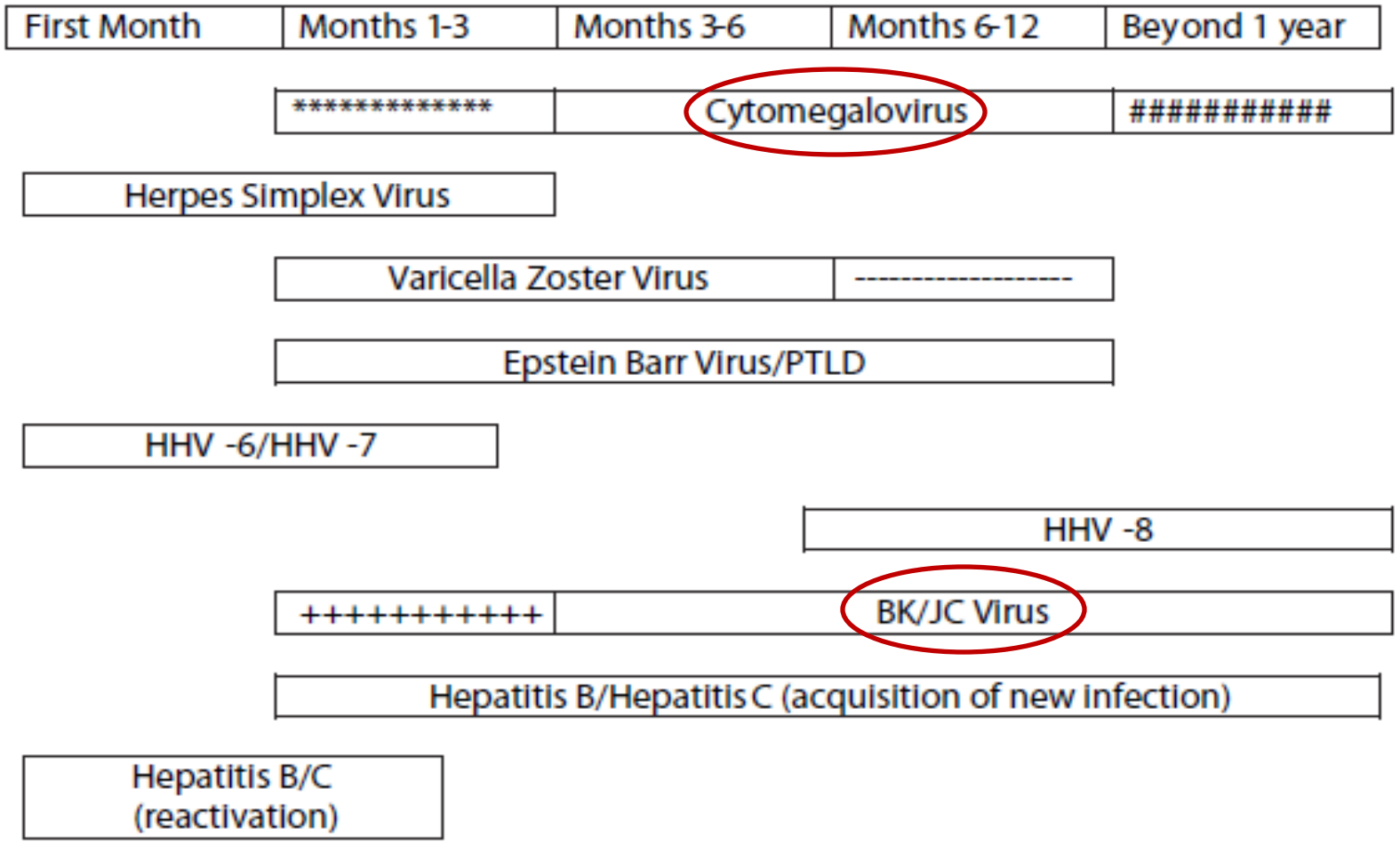
Timeline of Post transplant Infections



Viral Pathogens in Transplantation

- Herpes simplex
- Varicella zoster
- Epstein-Barr virus
- Cytomegalovirus
- HHV8
- HIV
- West Nile virus
- Rabies
- Hepatitis B and C
- Papillomavirus
- Polyomavirus Bk/JC
- Adenovirus
- Influenza, parainfluenza
- Parvovirus B19
- Smallpox/vaccinia
- SARS, Corona virus

Timeline of Post transplant Viral Infections



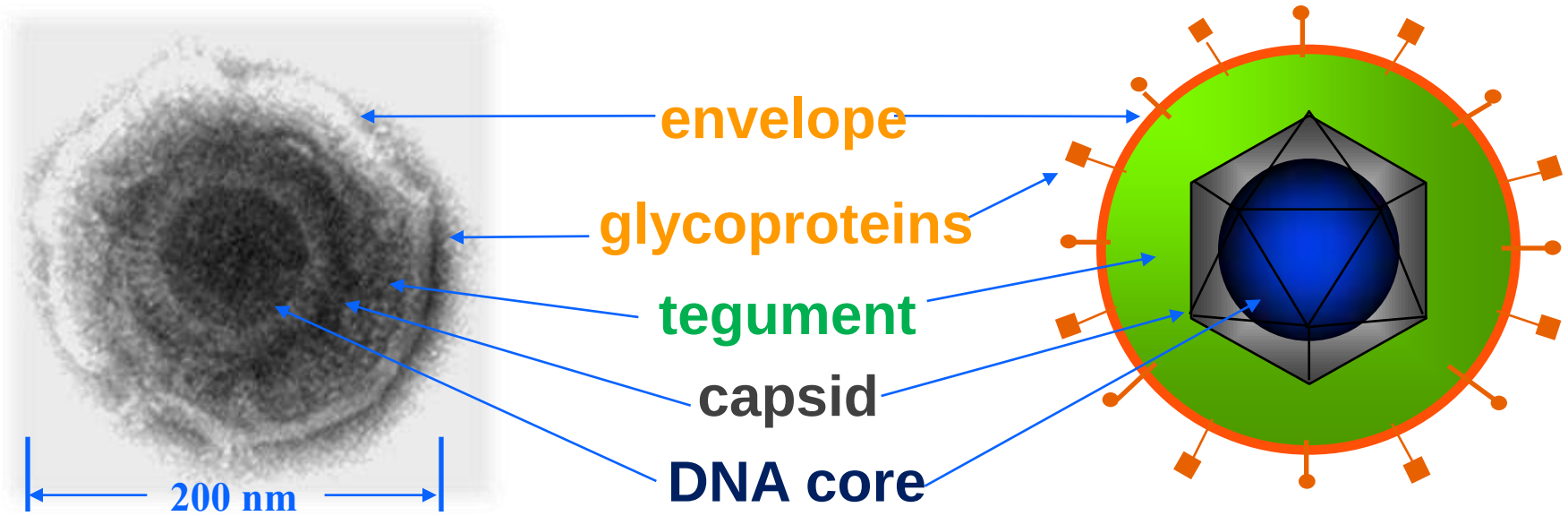
Weikert, B. C. et al. Clin J Am Soc Nephrol 2008;3:S76-S86

CJASN

CMV infection post renal transplant

Human Cytomegalovirus: structure

Human cytomegalovirus-human herpesvirus 5 (CMV) belongs to family Herpesviridae



Double-stranded, DNA herpesvirus that infects man and other species, producing unique large cells with inclusion bodies

CMV infection

- In immunocompentent individuals, most CMV infections are mild and may produce a viral syndrome

- Approximately 50 - 90% of immunocompetent adults >40 years old have antibodies (IgG) to CMV.

- In otherwise healthy adults, CMV remains inactive or latent, but ready to be become active under “favorable conditions”.

Risk Factors

- CMV status of donor and recipient.
- The number of CMV particles (viral load).
- Rate of increase of virus in the blood correlated with the risk of developing CMV disease.

Risk Factors

- Type of organ
  - Lung/small intestines **>** pancreas, heart **>** liver, kidney
  - Due to transplanted load; immune response in the allograft; level of immunosuppression

- Intensity of immunosuppression
  - Antilymphocyte products (e.g., thymoglobulin)
  - Dose, duration, and overall intensity of drugs
  - Newer agents – alemtuzumab, others?

CMV: mode of infection

- CMV is found in oropharyngeal secretions, urine, cervical and vaginal secretions, semen, breast milk, tissues and blood.
- It can be transmitted via transplanted tissue, blood transfusion, perinatally, and through sexual contact

Donor	Recipient	Type
D+	R-	primary
D-	R+	reactivation
D+	R+	superinfection
D-	R-	risk with exposure

CMV Infection: Risk Categories in Solid Organ Transplant Recipients

Risk Category	Donor (D) or Recipient (R) Seropositivity (+/-)
High	D+/R-
Intermediate*	D+/R+, D-/R+
Low	D-/R-

* D+/R+ generally at higher risk than D-/R+

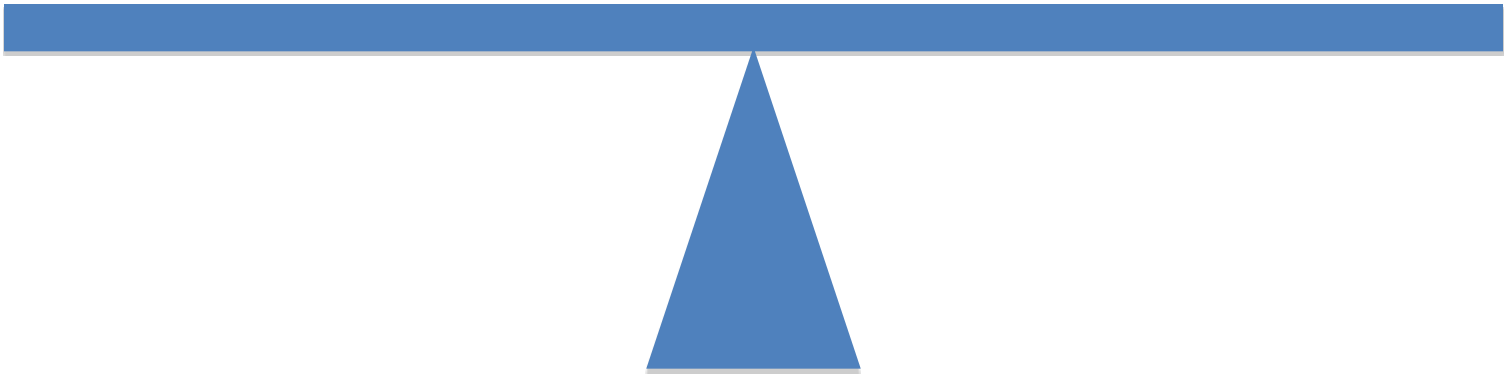
CMV Pathogenesis

Viral factors

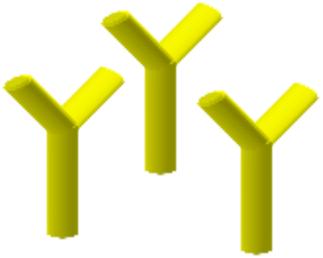
- Replication dynamics
- viral heterogeneity
- Viral co-infections

Host factors

- CD4+, CD8+ T-cell
- NK cell, B-cell
- exogenous immunosuppression
- D/R immune status

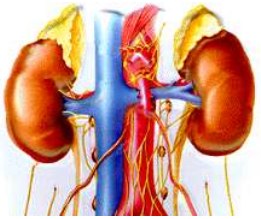


ANTILYMPHOCYTE ANTIBODIES

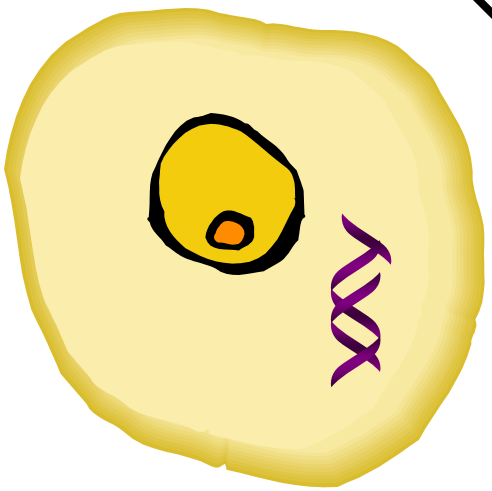


OTHER HERPES VIRUSES

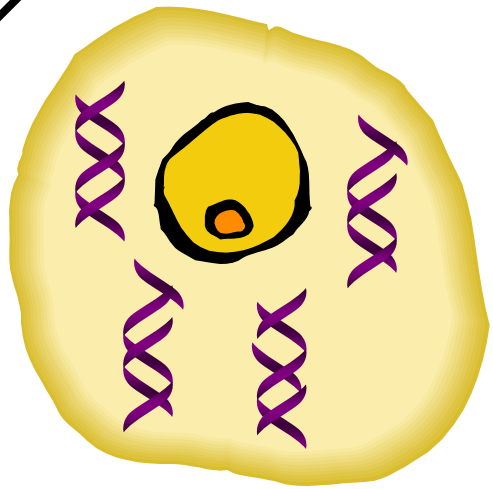
REJECTION



SEPSIS/ SURGERY



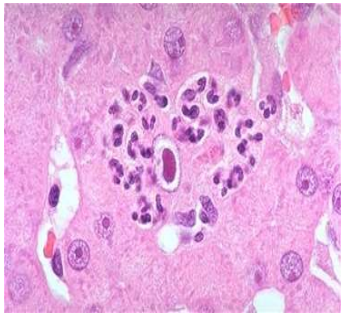
INFLAMMATION (CYTOKINES, NF-κB)



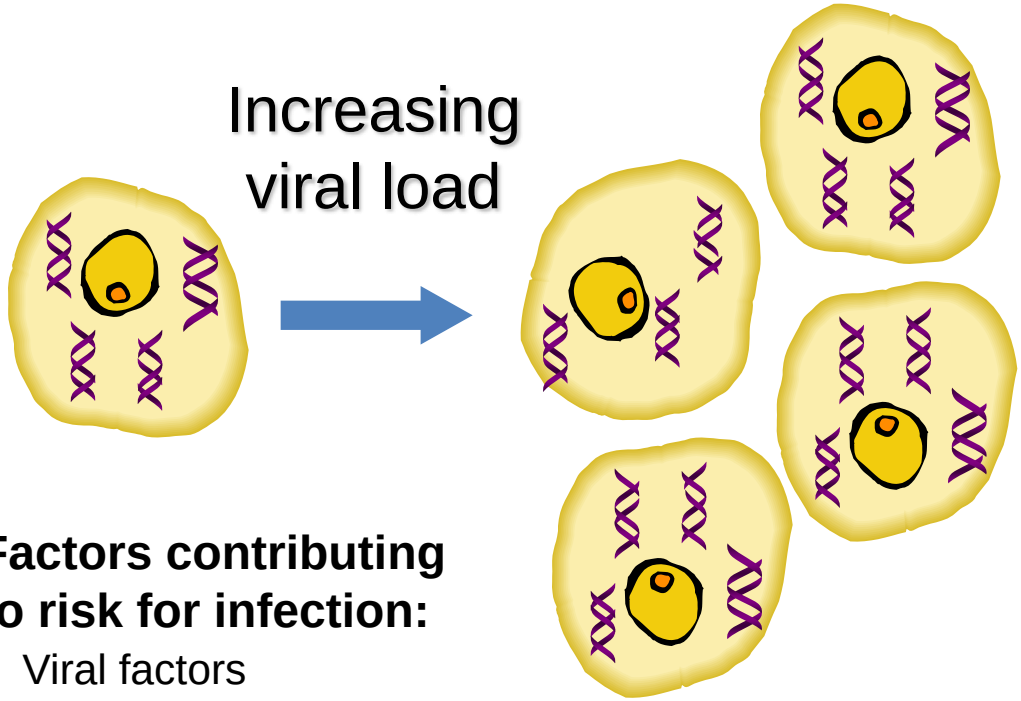
LATENT

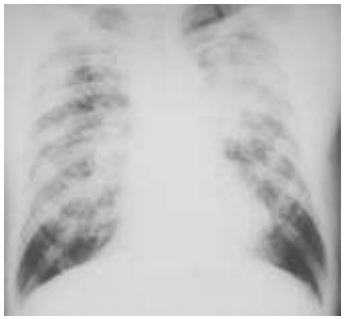
CMV INFECTION

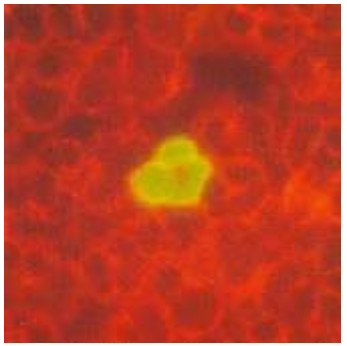
Co-Infection



Increasing viral load







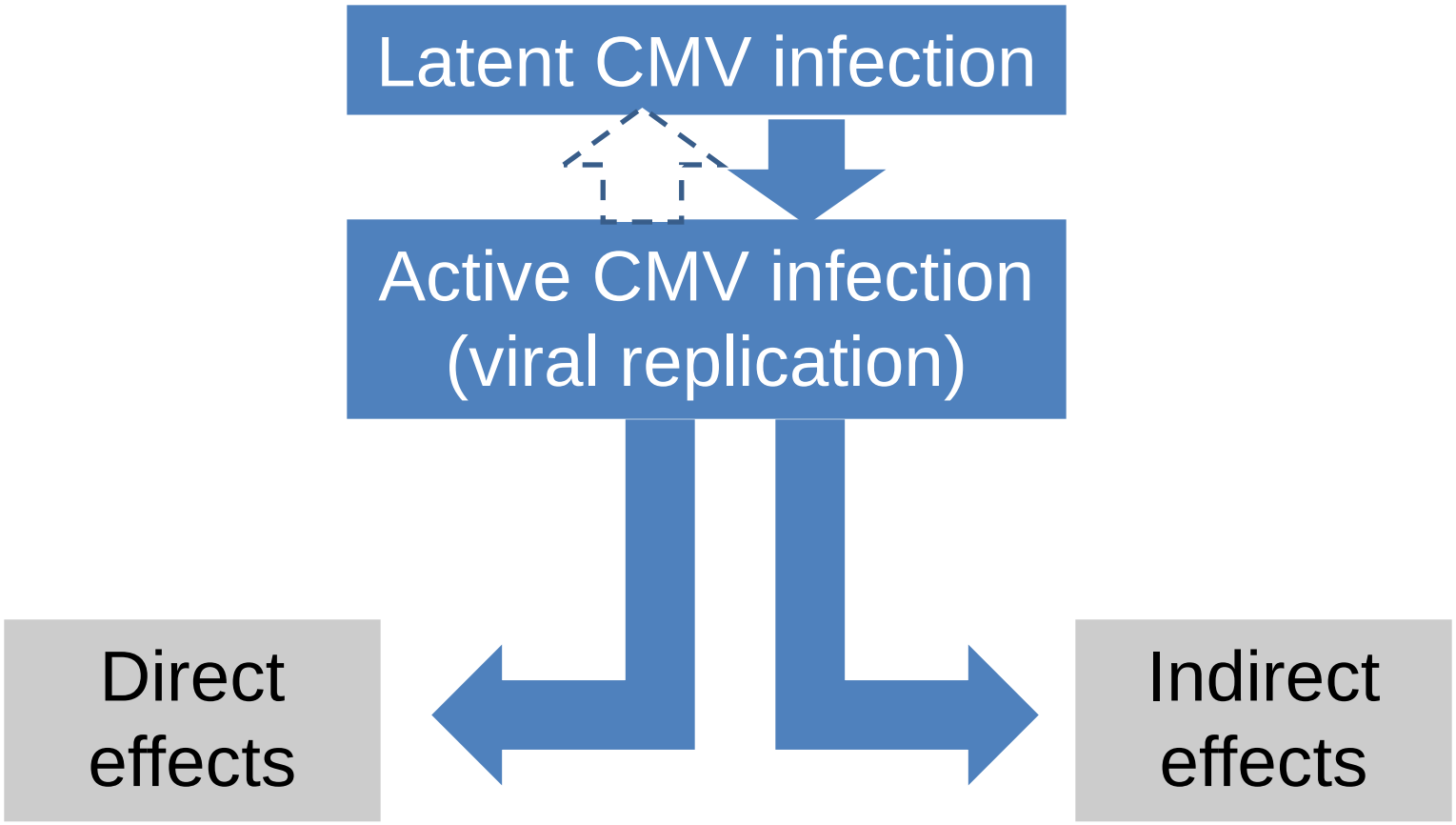
Factors contributing to risk for infection:

- Viral factors
- Immunosuppression
- Co-infection

CMV INFECTION

CMV DISEASE

CMV Infection



Direct Effects of CMV Infection

CMV Viral Syndrome

- Fever, malaise, myalgias
- Leukopenia, thrombocytopenia, and other laboratory abnormalities

Tissue Invasive Disease

- Hepatitis
- Pneumonitis
- Colitis
- Carditis
- Nephritis
- Pancreatitis
- Retinitis

Indirect Effects of CMV Infection

Indirect Effects

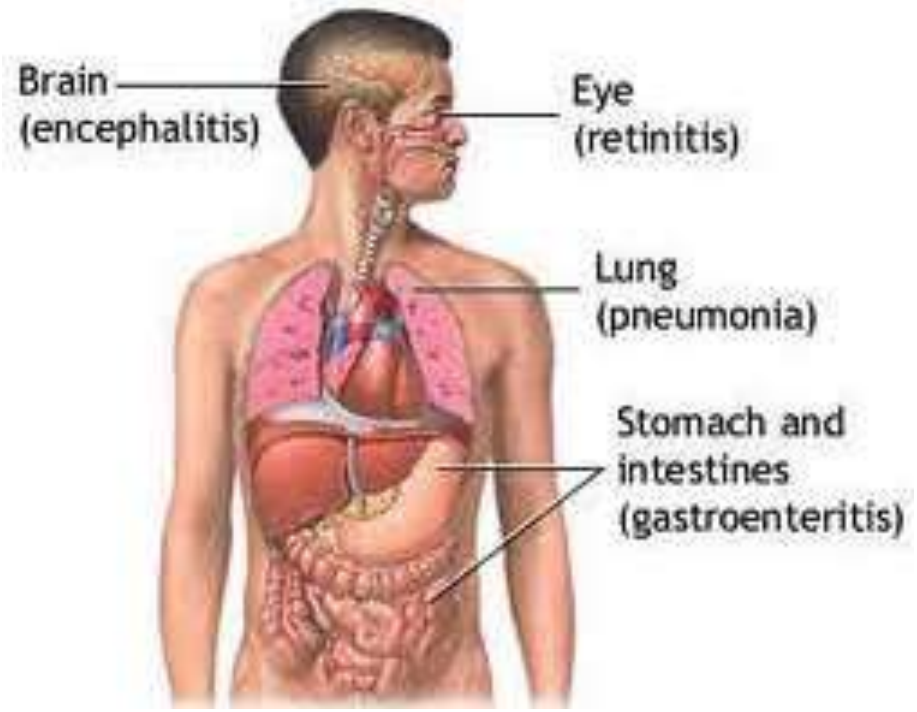
Altered host immune response

- Graft rejection; graft dysfunction
- Opportunistic infections: Bacterial fungal superinfection
- Decreased graft and patient survival
- Herpesvirus interactions: EBV/PTLD

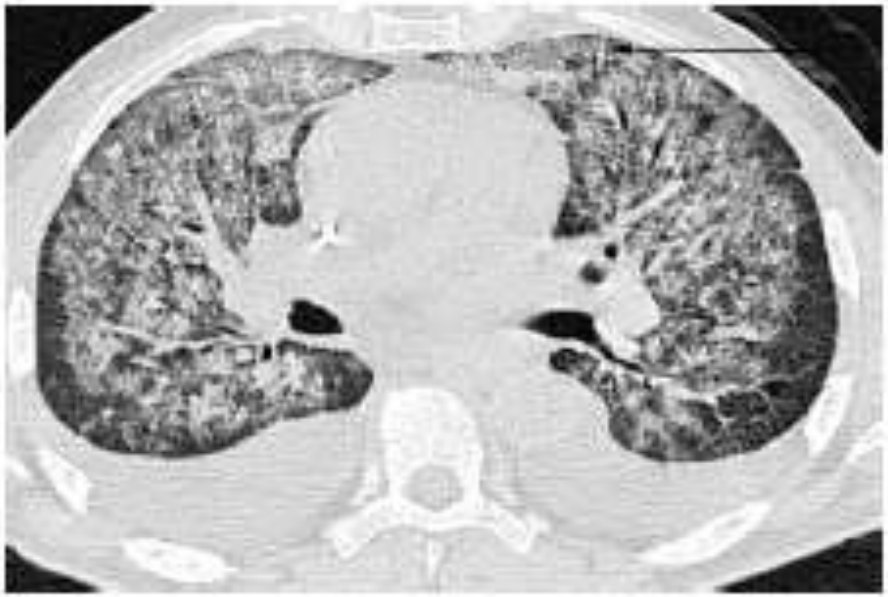
CMV Disease

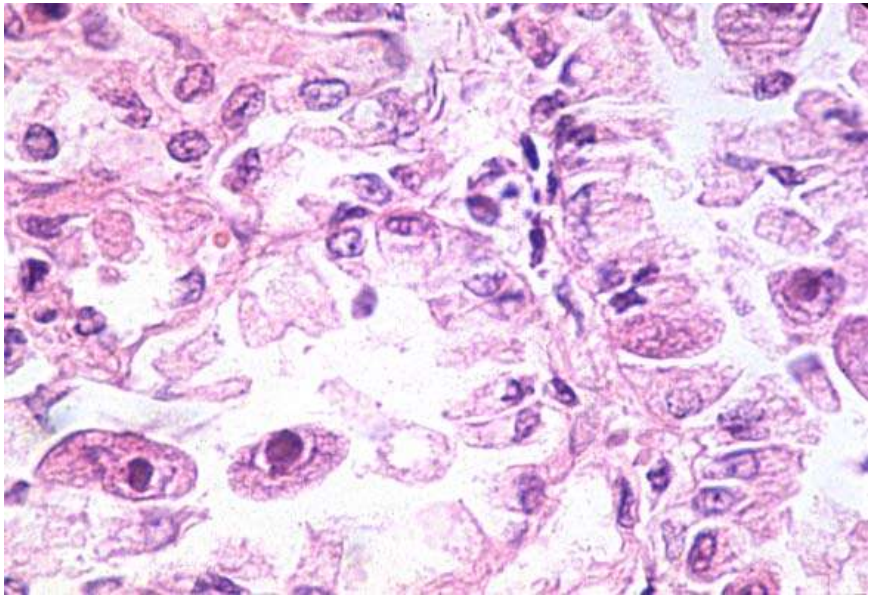
- CMV Infection + clinical signs and symptoms: fever, leukopenia, or organ involvement:

- Pneumonitis
- Esophagitis
- Encephalitis
- Hepatitis
- Pancreatitis
- Esophagitis
- Gastritis
- Retinitis

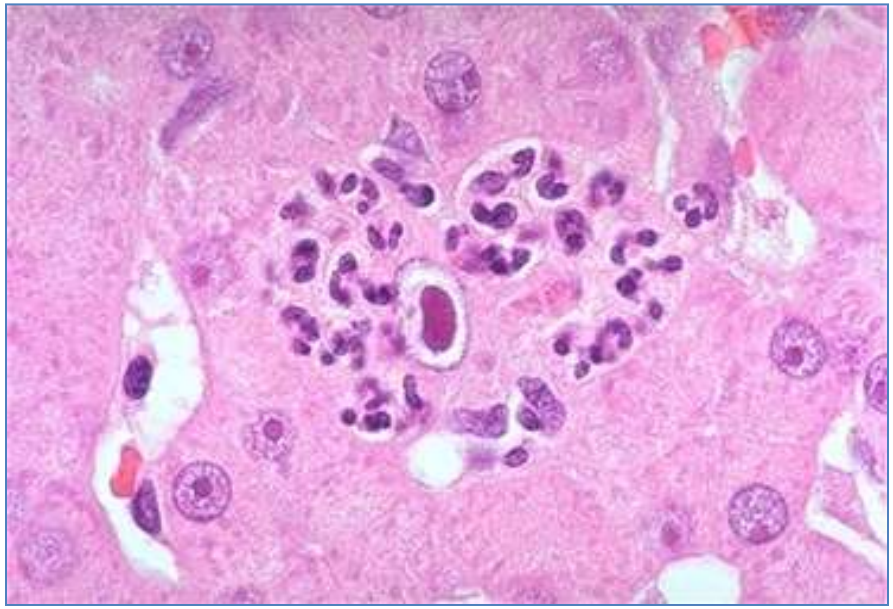


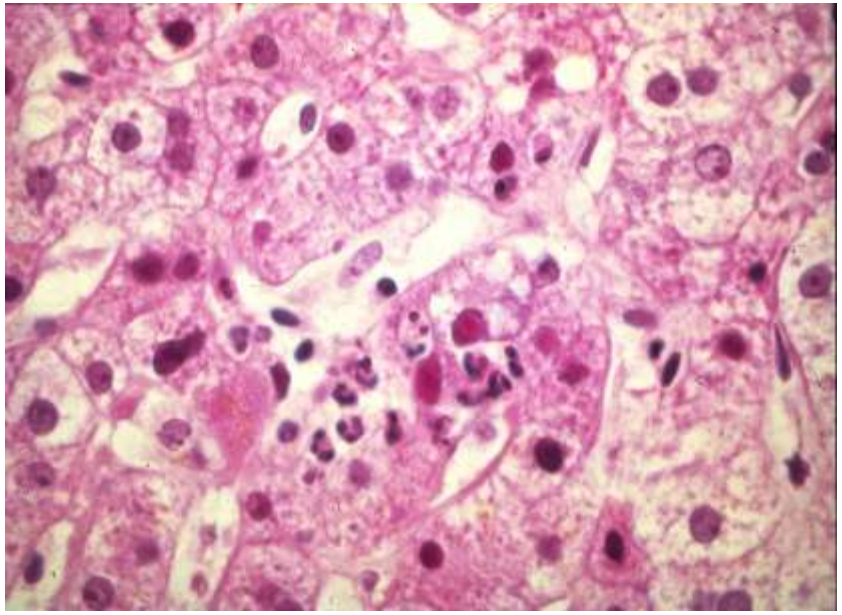
CMV Pneumonitis



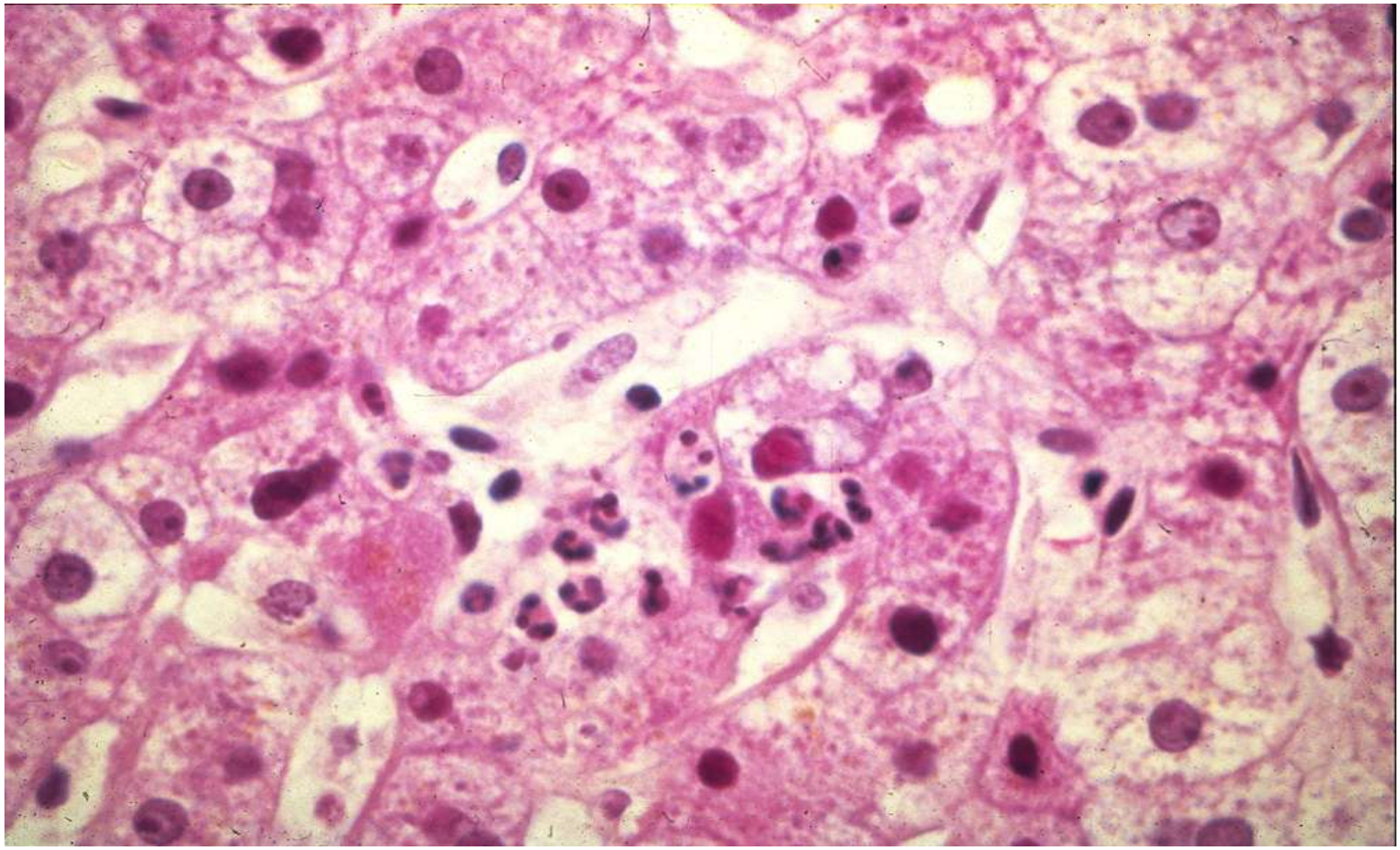


CMV Hepatitis

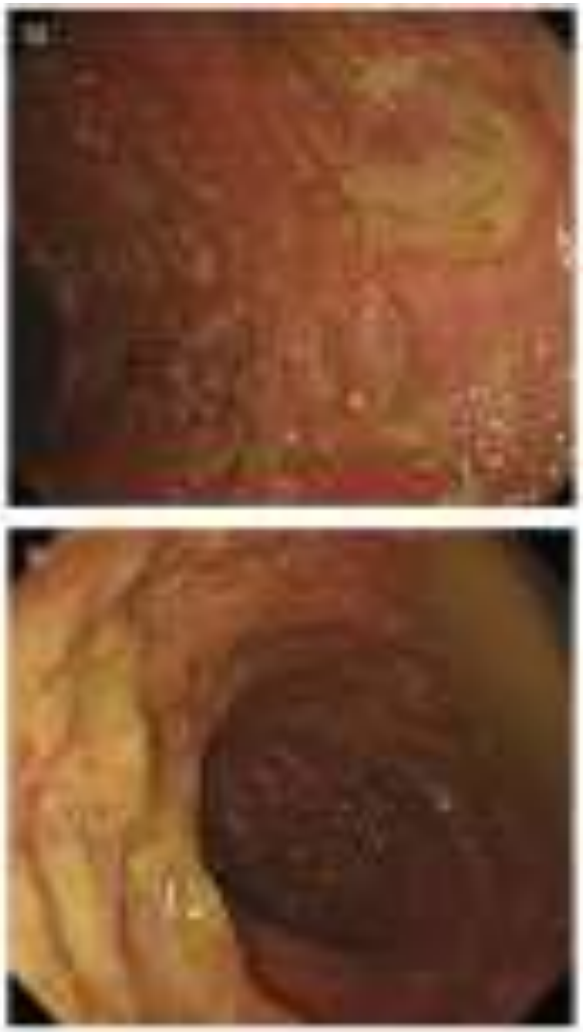


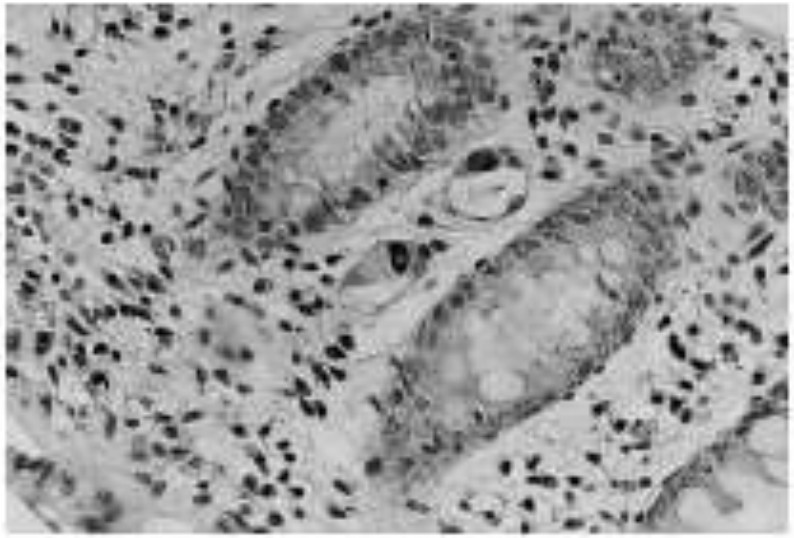


Microabscess Caused by CMV in the Liver

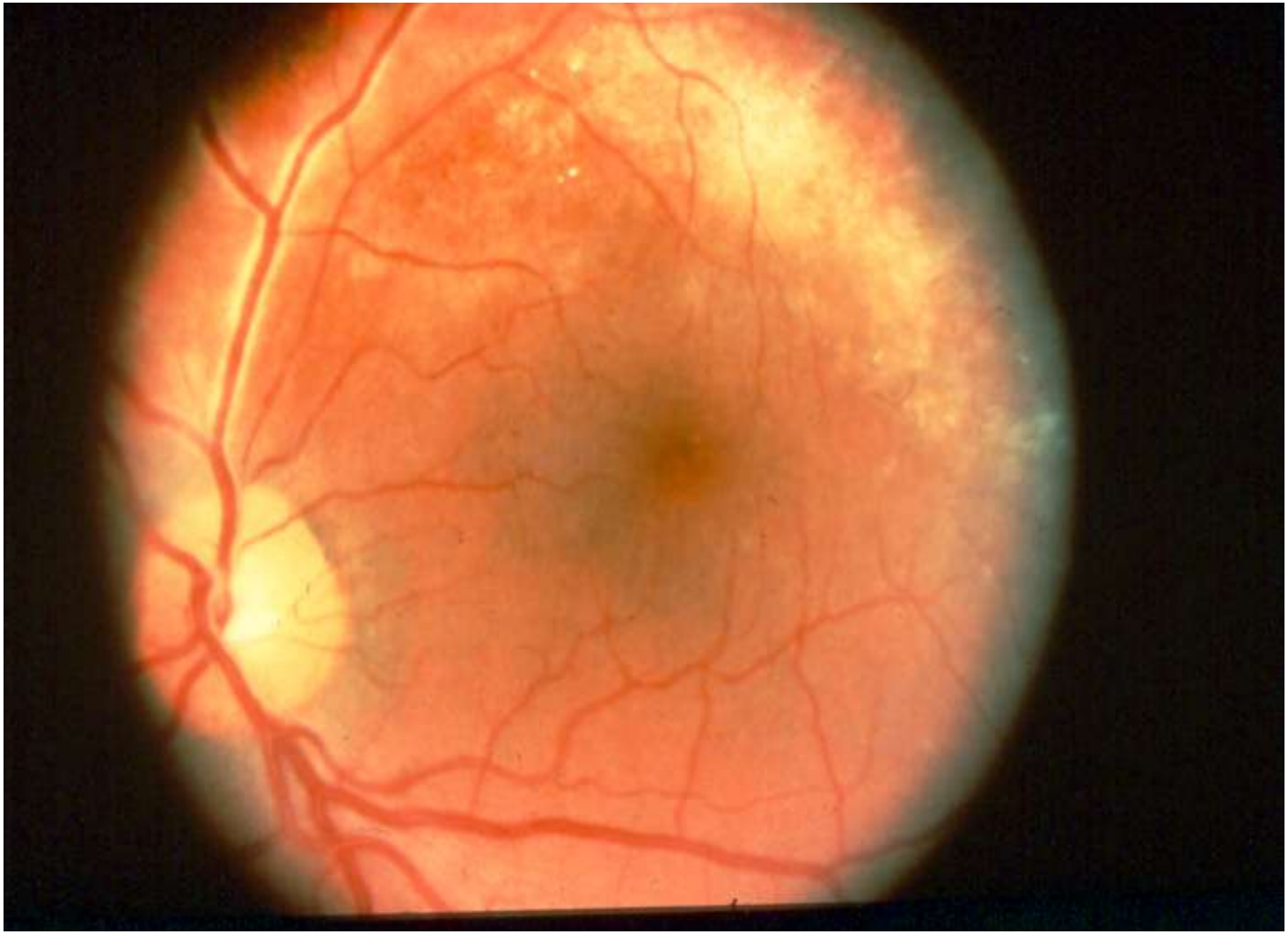


CMV Colitis





CMV Retinitis



CMV infection: diagnosis

- Seroconversion with the appearance of anti-CMV IgM antibodies.
- A fourfold increase in preexisting anti-CMV IgG titers.
- Detection of CMV antigens in infected cells.
- Detection of CMV-DNAemia by molecular techniques.
- Isolation of the virus by culture of the throat, buffy coat, or urine.

Optimal Strategies in the Management of CMV in Solid Organ Transplantation

CMV Prevention

- Pre-emptive
  - Guided by laboratory monitoring for evidence of early viral replication; treatment is started when CMV viral load or antigenemia reaches a certain threshold
- Universal prophylaxis
  - Therapy from the time of transplant to all patients or a subgroup of patients at risk for CMV disease

Pre-emptive strategy

- Blood quantitative CMV-PCR weekly for 3-4 monthspost transplant.
- CMV-PCR becomes positive, > 2000 copies/mL, approach varies in part upon the severity of the infection:

a) Stop AZA or MMF

b) Asymptomatic/Mild disease – valganciclovir for 21 days or longer if necessary to clear viremia.

c) Weekly quantitative PCRs should be obtained during treatment to determine response. If levels no less by 50% in two weeks, viral resistance should be suspected, Consider IV .

Pre-emptive Therapy

- **Advantages**:
  - Minimizes drug exposure
  - This may potentially decrease toxicity and costs
  - Theoretically lower risk of resistance
- **Disadvantages**:
  - Logistically more difficult to coordinate
  - May be unsuccessful in preventing progression to active disease in high-risk patients due to rapid doubling time.
  - May not eliminate the indirect effects of CMV

Antiviral Prophylaxis

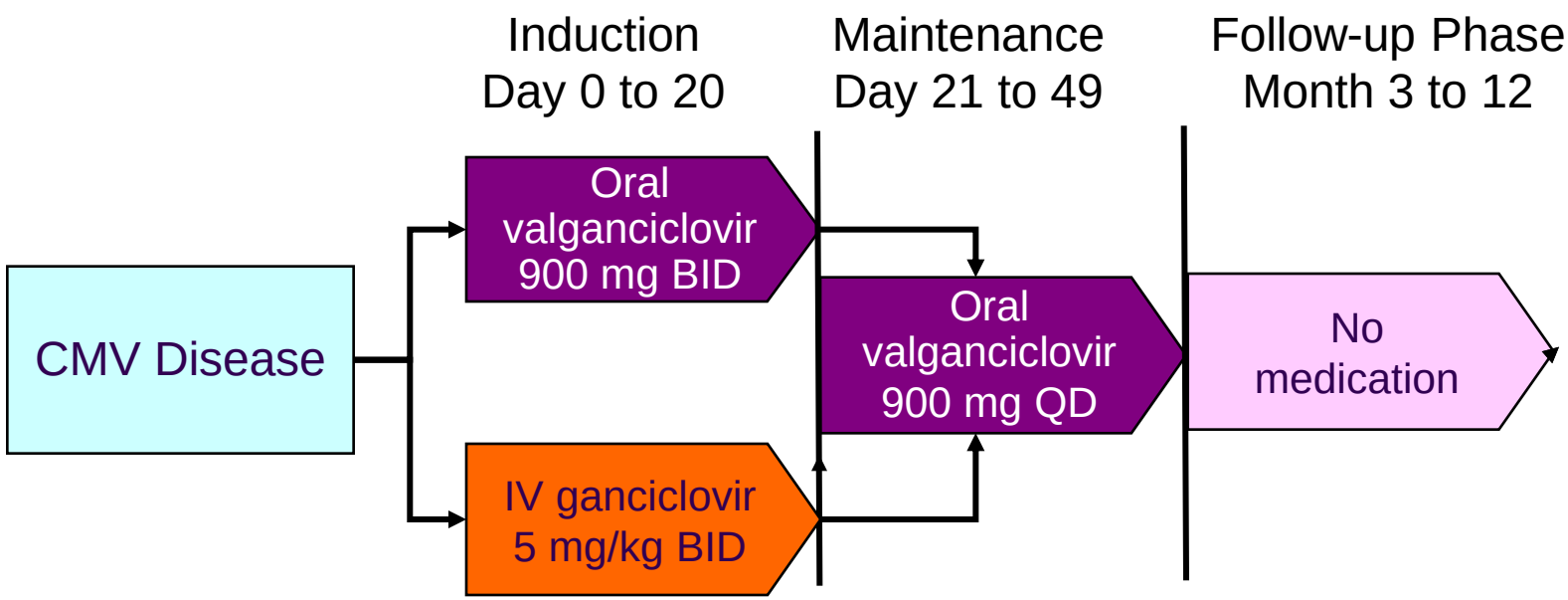
- Antiviral therapy from the time of transplant to all patients or a subgroup of patients (universal or targeted)
- **Advantages**:
  - Proven efficacy
  - Decreases indirect effects
  - Ease of administration
- **Disadvantages**:
  - Drug toxicity
  - cost
  - Resistance

Antiviral Prophylaxis: choice and duration

- D-/R- : acyclovir for 3 months
- D-/R+ :valganciclovir for 3 - 6 months
- D+/R+ and D+/R- : valganciclovir for 6 - 9 months.

The worst graft and patient survival at three years post-transplantation is observed among the group in which the donor and recipient are both positive.

Treatment of CMV: Oral vs. IV



Anti-CMV Therapy

- **Ganciclovir:** (Cymevene®) competitively inhibits the incorporation of dGTP by viral DNA polymerase–intravenous or oral.

- **Valganciclovir:** (Valcyte®) a prodrug form of ganciclovir with improved oral bioavailability.

- **Foscarnet:** (Foscavir®) is an inhibitor CMV DNA polymerase
  - Useful for ganciclovir-resistant CMV
  - Major limitation is nephrotoxicity

- **Cidofovir:** (Vistide®) inhibits viral DNA polymerase
  - May be useful for ganciclovir-resistant CMV but not well studied in organ transplant recipients

- **Maribavir:** is an investigational agent that prevents viral encapsidation and nuclear egress

Ganciclovir

- **Pharmacokinetics:**
  - Oral ganciclovir: poor absorption – (~ 5% fasting and ~ 8% with food)
  - 90% of plasma ganciclovir is eliminated unchanged in the urine with a half-life of 2-6 hrs, depending on renal function

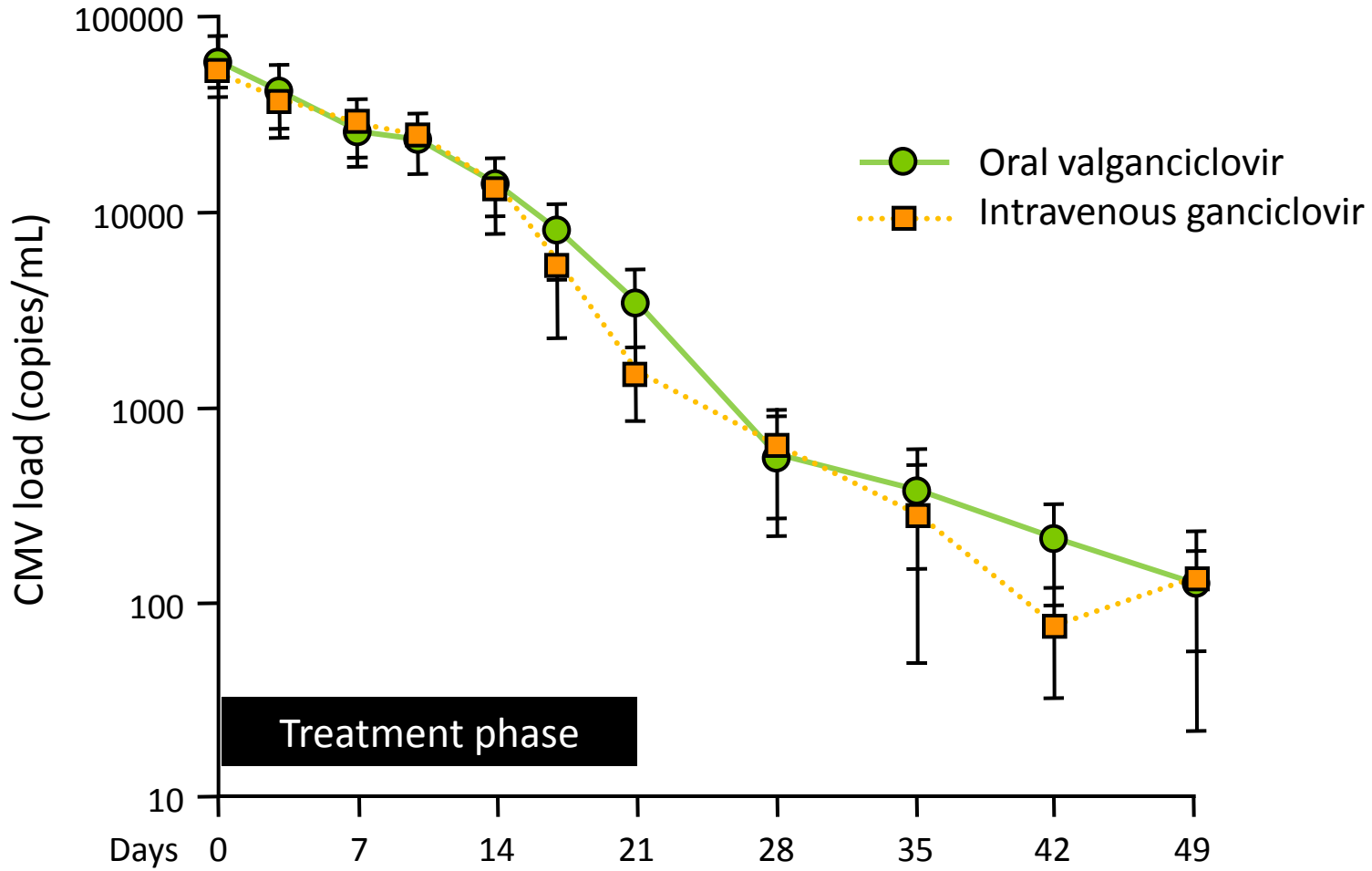
- **Adverse effects:**
  - Hematologic: neutropenia, anemia, thrombocytopenia
  - Gastrointestinal: nausea, vomiting, diarrhea, abdominal pain, flatulence, anorexia
  - Neurologic: headache, confusion, hallucination, seizures
  - Other: pain and phlebitis at injection site (due to high pH), sweating, rash, itch, increased serum creatinine and blood urea concentrations

Valganciclovir

- **Pharmacokinetics:**
  - Oral bioavailability ~ 60%
  - Eliminated as ganciclovir in the urine, with a half-life of about 4 hours

- **Adverse effects:**
  - Similar to ganciclovir
  - Myelosuppression is one of the main side effects that may limit prolonged use of valganciclovir

Cytomegalovirus Clearance Kinetics



Valganciclovir (N)	133	130	128	123	123	124	124	122	118	115	117
Ganciclovir (N)	125	122	123	123	124	121	120	120	119	118	116

Asberg, et al. *AJT*. 2007;7(9):2106-2113.

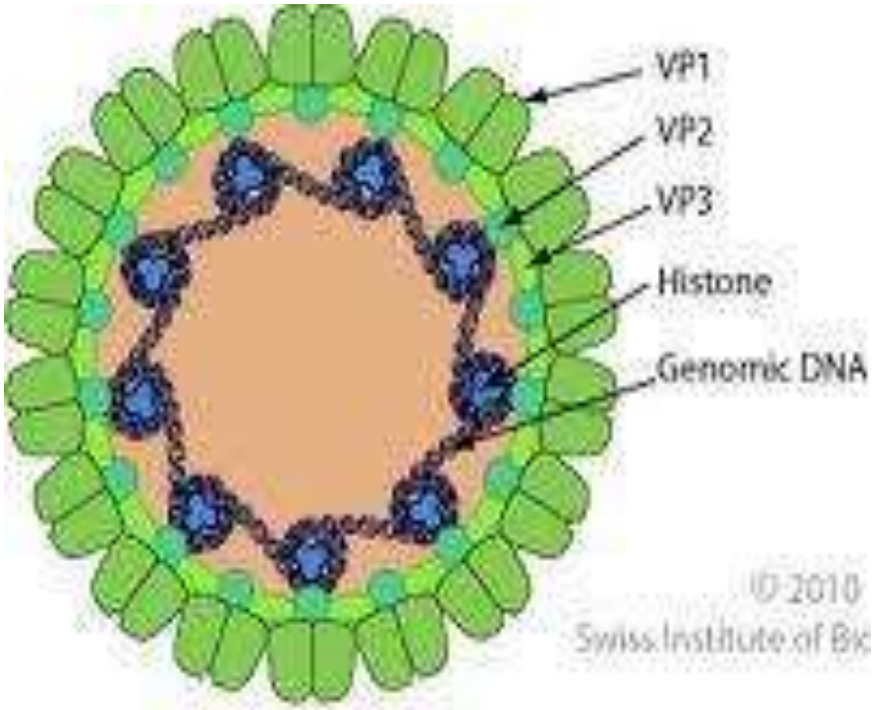
CMV: Take home message

- CMV is the most common and single most important viral infection in solid organ transplant recipients.
- CMV-positive patients had significantly higher incidence of CMV disease, allograft loss, and overall costs compared with CMV-negative recipients.
- In the absence of prophylaxis, CMV reactivation can occur in over 75% of solid organ transplant recipients depending on other risk factors
- up to 30% of patients may develop disease after stopping prophylaxis
- Once CMV infection is established, then its replication is highly dynamic with rapid increases in viral load

BK virus infection post renal transplant

BKV infection: the virus

- DNA virus that belongs to the polyomaviridae family:
  - Polyomavirus BK
  - Polyomavirus JC
  - SV40



The story of BKVN

- First reported in a renal transplant patient, BK Virus, in 1971.

The First report

New human papovavirus (b.K.) Isolated from urine after renal transplantation

SylviaD. Gardner a b, AnneM. Field a b, DulcieV. Coleman b, B. Hulme b
The Lancet, Volume 297, Issue 7712, Pages 1253 - 1257, 19 June 1971

The isolation of a new papovavirus from the urine of a renal allograft recipient with ureteric obstruction is described. Virus particles were observed in the cells lining the ureter by electron microscopy, and high, rising antibody titers to the virus were demonstrated in the patient's serum.

This virus is not identical with any of the previously described members of the polyoma subgroup and has provisionally been named B.K. virus after the patient.

History of BKVN

- First reported in a renal transplant patient, BK, in 1971.

- No reported cases of this disease for the next 24 years, until Purighalla and co-workers observed their first case in early 1995.

History of BKVN

RENAL BIOPSY CASE

BK Virus Infection in a Kidney Allograft Diagnosed by Needle Biopsy

Raman Purighalla, MBBS, Ron Shapiro, MD, Jerry McCauley, MD, and Parmjeet Randhawa, MD

American Journal of Kidney Diseases, Vol 26, No 4 (October), 1995: pp 671-673

History of BKVN

- First reported in a renal transplant patient, BK, in 1971.
- No reported cases of this disease for the next 24 years, until Purighalla and co-workers observed their first case in early 1995.
- Subsequently there has been a surge in reported cases worldwide.

Epidemiology of BKV infection

- Approx. 80% of the general population has a detectable antibody to BKV, which appears early in life and remains elevated throughout life.

- Primary Infection occurs in early life when it is either asymptomatic or with mild URTI. Thereafter BKV largely persists in the kidneys and urinary tract in a latent form.

- The principal routes of transmission are fecal-oral, respiratory, transplacental, or from donor tissue.

J Gen Virol 2003; 84: 1499–1504

Source of infection

Two proposed hypotheses:

1. Transmission occurs through the donor kidney.
2. Reactivation in the recipient renal epithelium after transplantation.

Risk factors

- Risk factors:
  - Older, male, White, diabetic recipient
  - More HLA mm, ACR, DGF

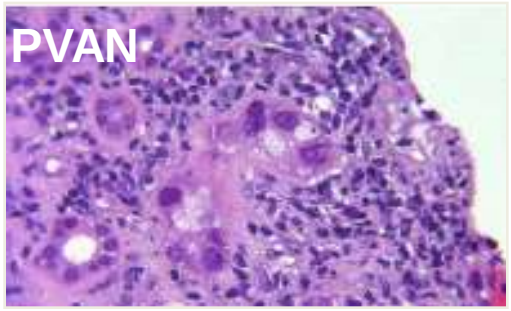
- States of immune suppression
  - Pregnancy
  - Malignancy
  - HIV
  - Diabetes
  - Transplantation

BKV nephropathy after kidney Tx: pathogenesis

Renal injury
+
organ BK load
BKV mutations

↑ BKV replication

BKV-mediated tissue damage



Immunosuppression load

±

BK seronegativity

Failure of immune surveillance

Role of Immunosuppressive medications

- Prior to 1995; when Tac and MMF were introduced, BKVAN was a rare entity.

- Reduction or pre-emptive withdrawal of immunosuppressive medication was associated with BKV clearance.

- The occurrence of BKVN is not due to specific immunosuppressive agents, but may be related to the overall degree of immunosuppression.

Onset of post Tx BKV infection

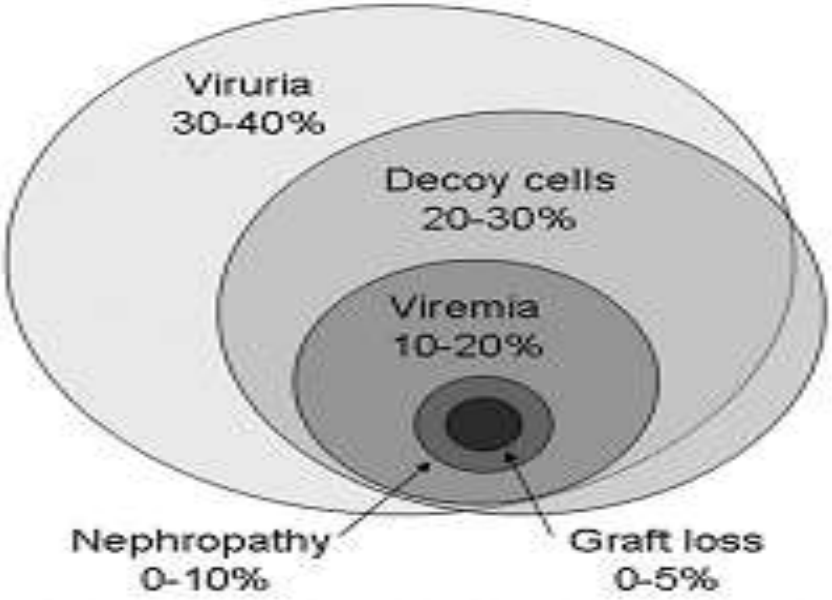
- 50% of patients who develop BK viremia do so by 3 months after kidney transplantation.

- 95% of BKV nephropathy occurs in the first 2 years after kidney transplantation.

Clinical Features of BKV infection

- Most renal transplant recipients with BKVN manifest with renal dysfunction.
- Progressive renal failure has been reported in approximately 30–60% of cases.
- Occasionally, subjects can also present with ureteric obstruction and hydronephrosis.

Clinical Features of BKV infection



*Rare cases of nephropathy without viremia or viremia without viruria may occur

Type and prevalence of BK virus (BKV) infections in kidney transplant recipients.

Clin J Am Soc Nephrol 2007;2: S36–S46

Outcome of BKVN

- Approximately 40–60% of renal grafts with BKVN develop progressive graft loss.

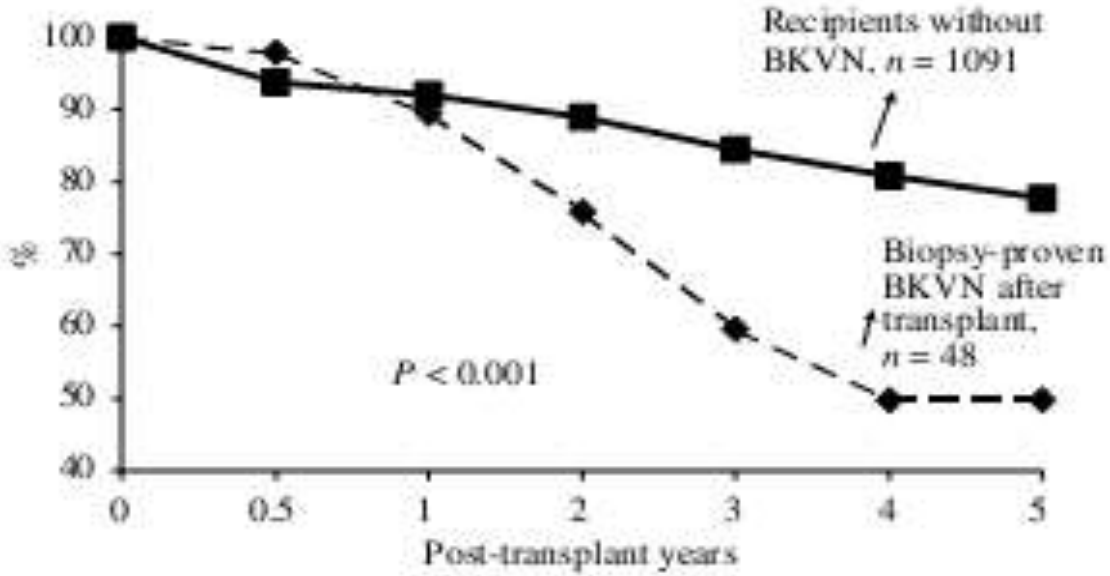
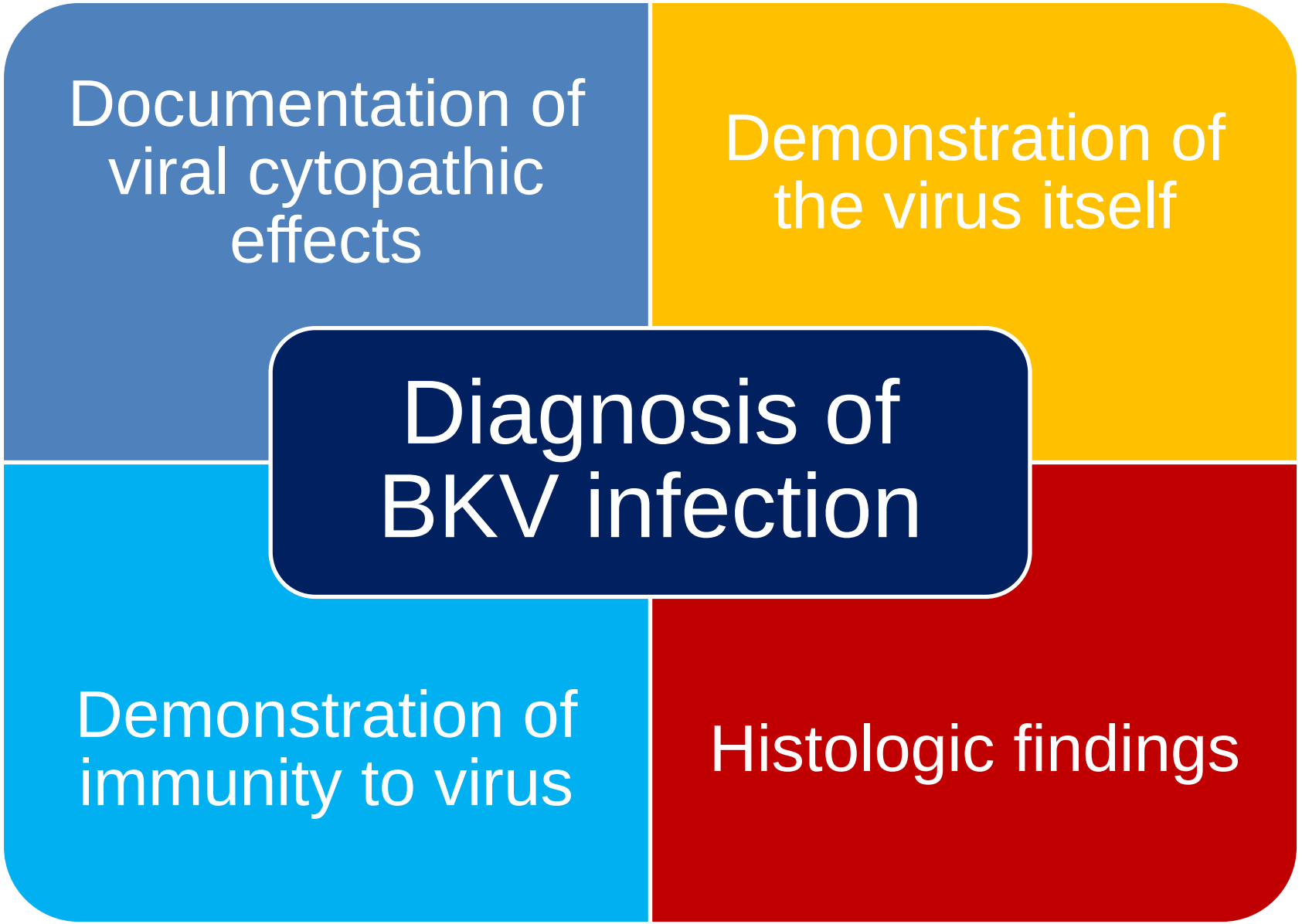


Figure 3 | Lower actuarial graft survival rates in patients with BKVN – results from the Medical College of Wisconsin 1996–2004.


Documentation of viral cytopathic effects
Demonstration of the virus itself
Diagnosis of BKV infection
Demonstration of immunity to virus
Histologic findings

Diagnosis of BKVN

DIAGNOSIS

- Renal biopsy
- Urinary cytology
- Measurement of BKV-DNA in blood and urine (by real time PCR)

Diagnosis of BKVN

Tests	Findings	Comments
Urine cytology	Presence of decoy cells	Seen in 40-60% of transplant recipients, good screening test, positive predictive value around 20%

Diagnosis of BKVN

Tests	Findings	Comments
Urine cytology	Presence of decoy cells	Seen in 40-60% of transplant recipients, good screening test, positive predictive value around 20%
Viremia (plasma BKV DNA)	Copies > 7000 per ml of plasma	Seen in 10–20% of transplant recipients, good

Diagnosis of BKVN

Tests	Findings	Comments
Urine cytology	Presence of decoy cells	Seen in 40-60% of transplant recipients, good screening test, positive predictive value around 20%
Viremia (plasma BKV DNA)	Copies > 7000 per ml of plasma	Seen in 10–20% of transplant recipients, good screening test, positive predictive value around 60%
Viruria (urinary BKV DNA)	Copies 100-fold higher than plasma values	Seen in 30-40% of transplant recipients, good screening test, positive predictive value around 40%

Diagnosis of BKVN

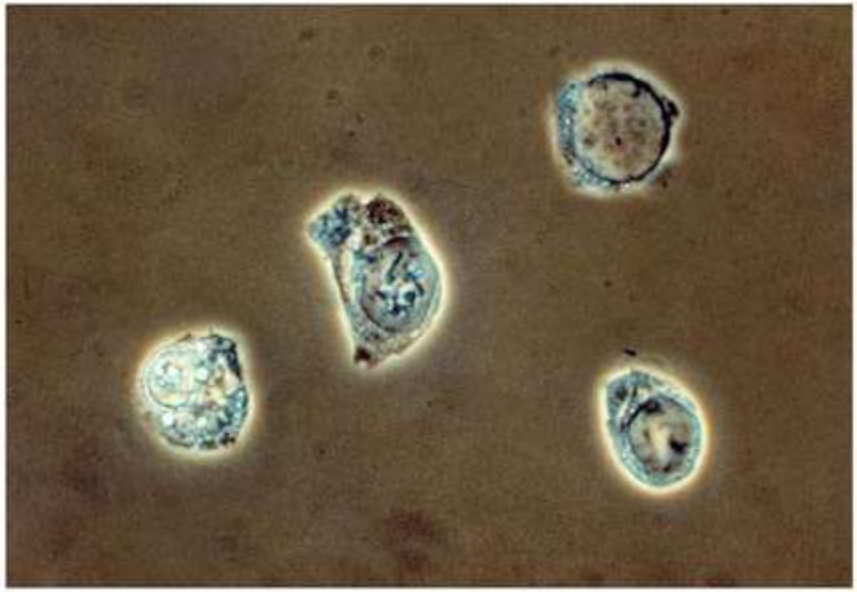
Tests	Findings	Comments
Urine cytology	Presence of decoy cells	Seen in 40-60% of transplant recipients, good screening test, positive predictive value around 20%
Viremia (plasma BKV DNA)	Copies > 7000 per ml of plasma	Seen in 10–20% of transplant recipients, good screening test, positive predictive value around 60%
Viruria (urinary BKV DNA)	Copies 100-fold higher than plasma values	Seen in 30-40% of transplant recipients, good screening test, positive predictive value around 40%
BKV DNA in renal tissue	Detection of BKV DNA in renal biopsy tissue	Negative predictive value 100%, positive predictive value around 70%

Diagnosis of BKVN

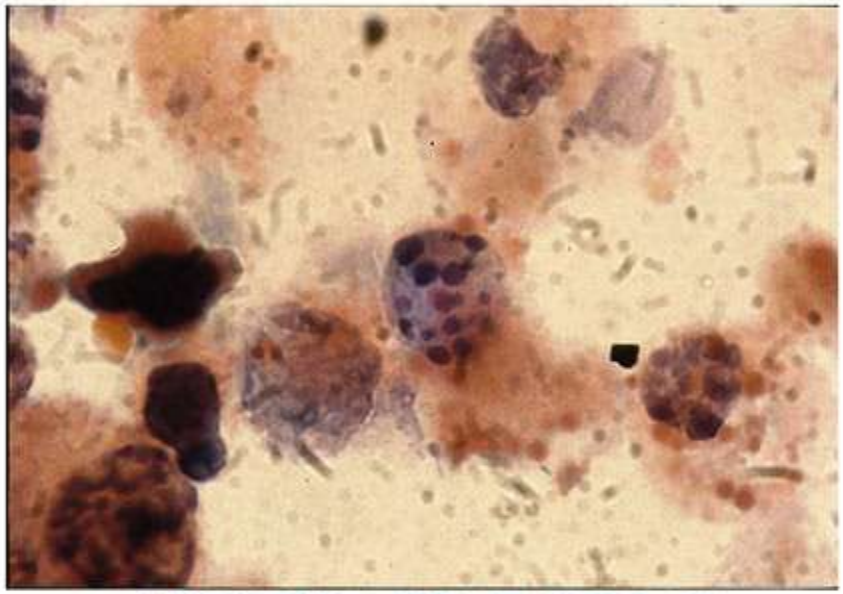
Tests	Findings	Comments
Urine cytology	Presence of decoy cells	Seen in 40-60% of transplant recipients, good screening test, positive predictive value around 20%
Viremia (plasma BKV DNA)	Copies > 7000 per ml of plasma	Seen in 10–20% of transplant recipients, good screening test, positive predictive value around 60%
Viruria (urinary BKV DNA)	Copies 100-fold higher than plasma values	Seen in 30-40% of transplant recipients, good screening test, positive predictive value around 40%
BKV DNA in renal tissue	Detection of BKV DNA in renal biopsy tissue	Negative predictive value 100%, positive predictive value around 70%
Renal histology	Inflammatory changes with viral cytopathic effects, positive immunoperoxidase reaction with SV40 stain, predominant CD20-positive lymphocytic infiltrates	Gold standard, invasive procedure, focal lesions, chronic state with minimal viral cytopathic effects, mimics acute rejection

Urine cytology in BKV infection: Decoy cells

Decoy cells are renal tubular or urothelial cells with intranuclear BKV-bearing inclusion bodies.

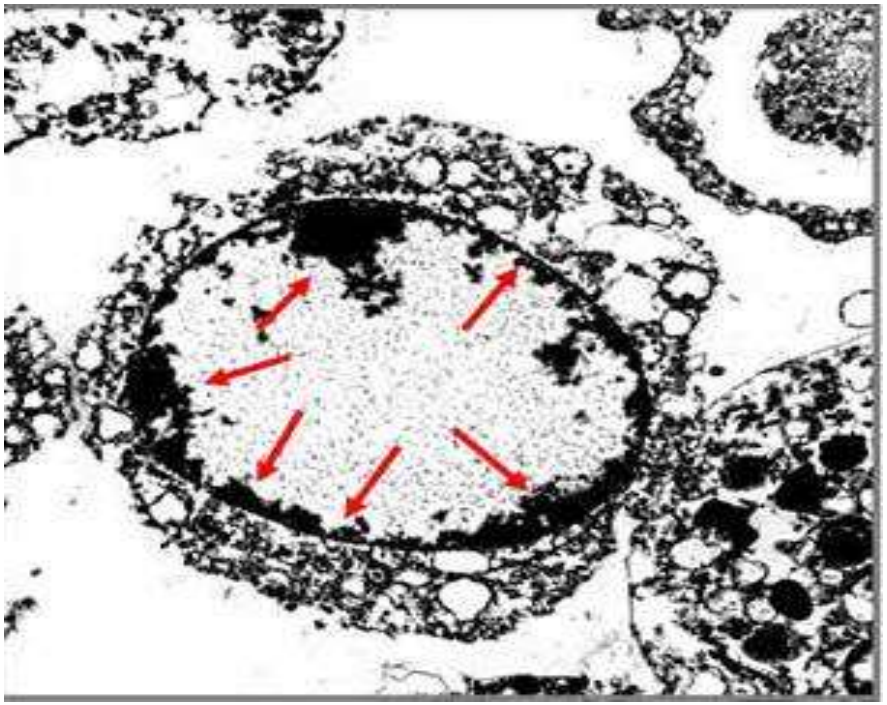


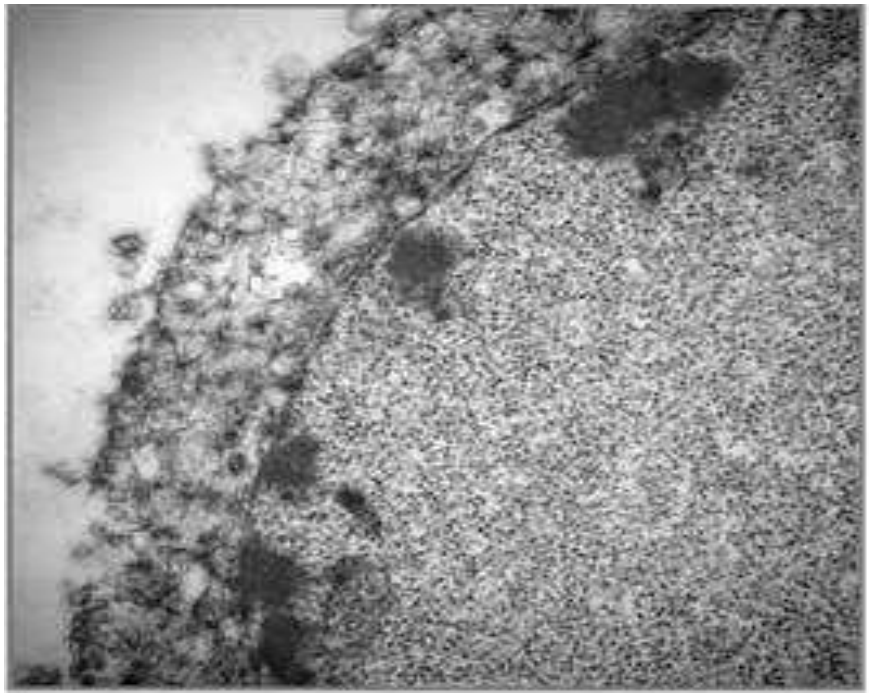
DECOY CELLS BY PHASE CONTRAST



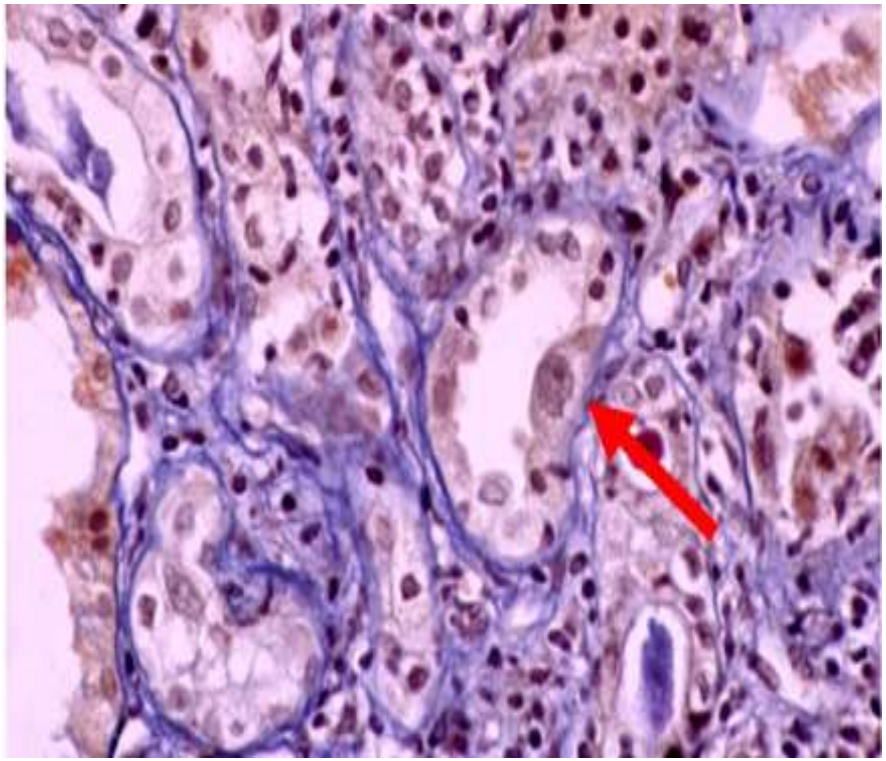
DECOY CELLS BY PAPANICOLAOU

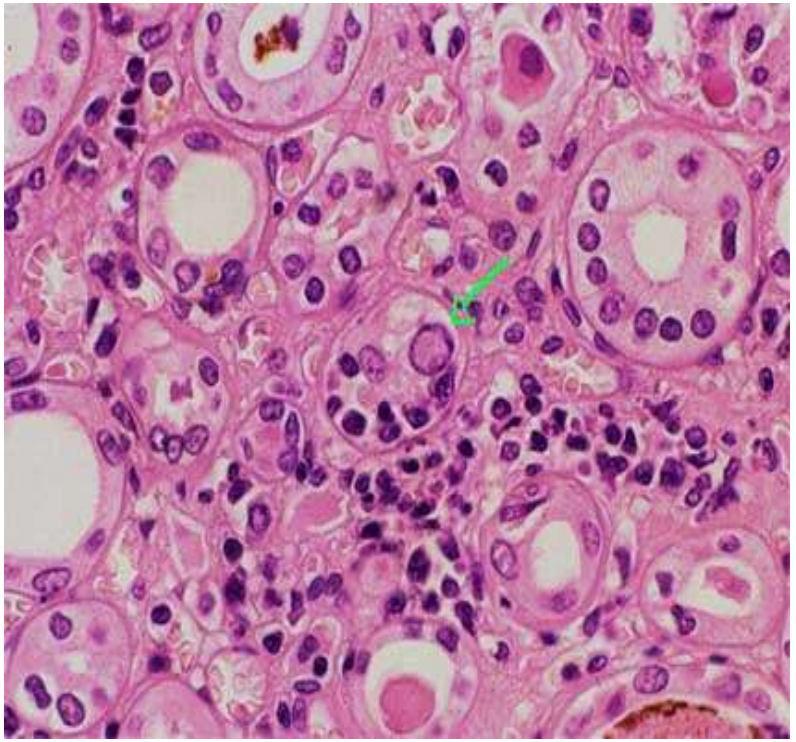
Urine cytology in BKV infection: Decoy cells





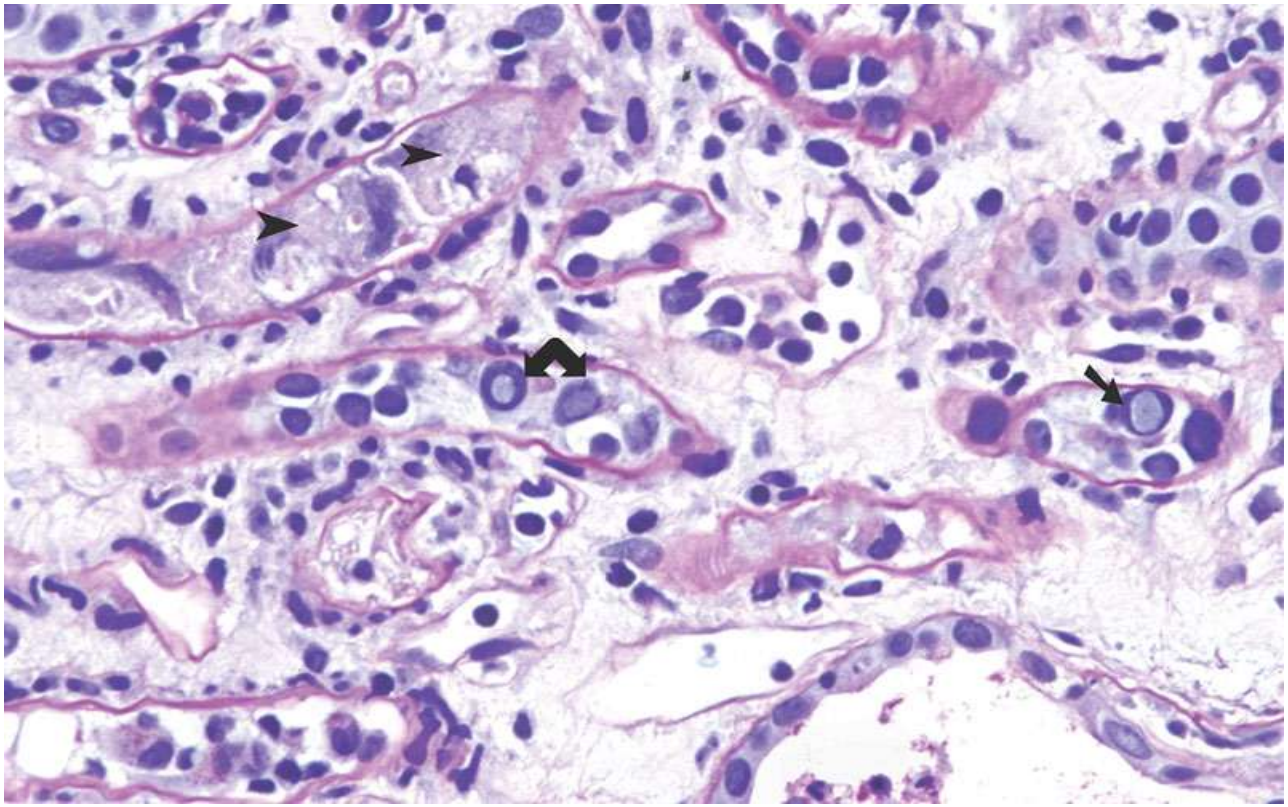
Histology of BKVN





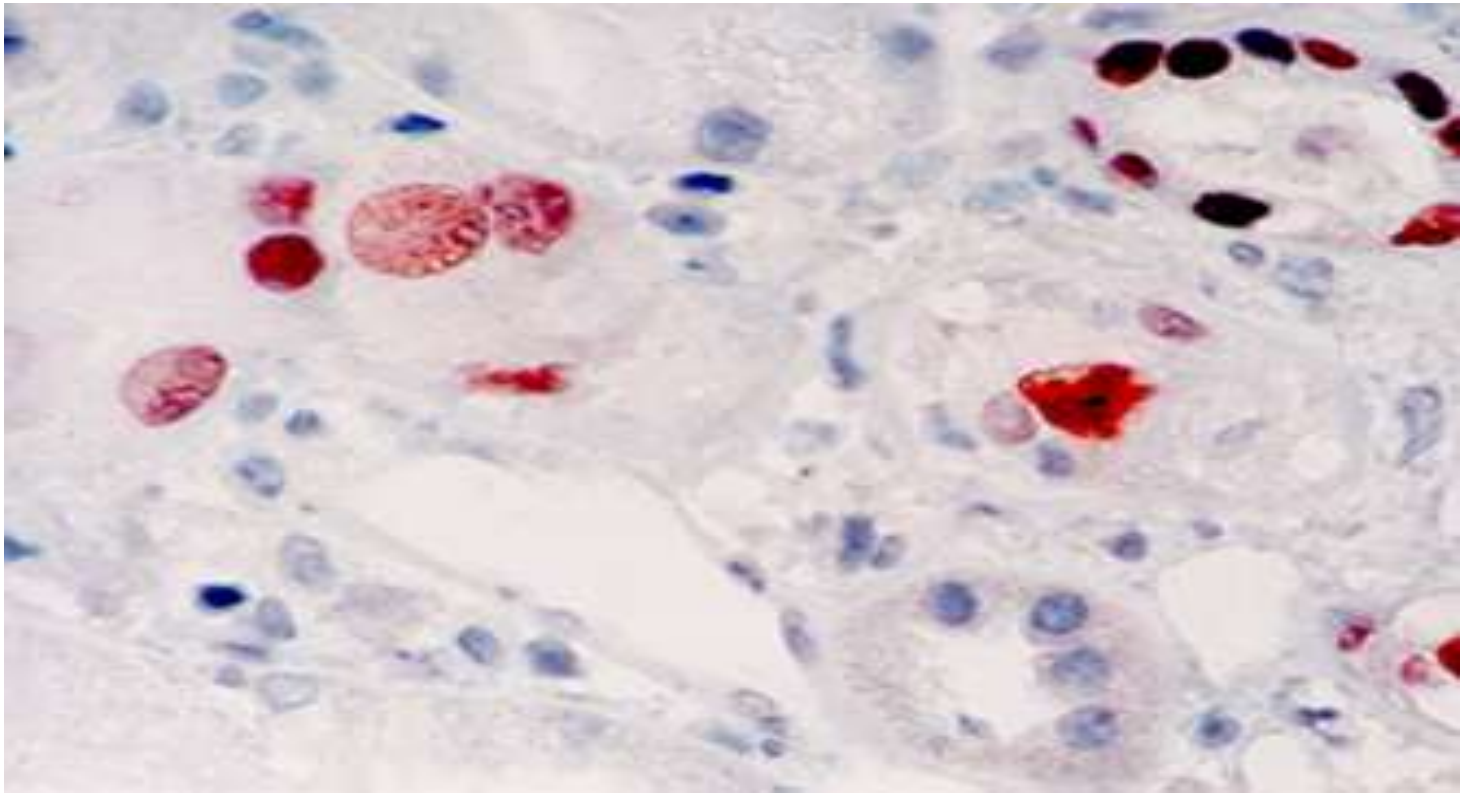
A typical tubular cell infected by polyoma virus BK

Histology of BKVN



A typical tubular cell infected by polyoma virus BK

Histology of BKVN



BK Virus: Immunoperoxidase Stain for SV-40

Current screening guidelines (KDIGO)

- Screen all kidney transplant patients for BKV using quantitative PCR of serum or plasma samples at the following time points:
  - Monthly for the first 3–6 months after transplantation, then every 3 months until the end of the first post-transplantation year.

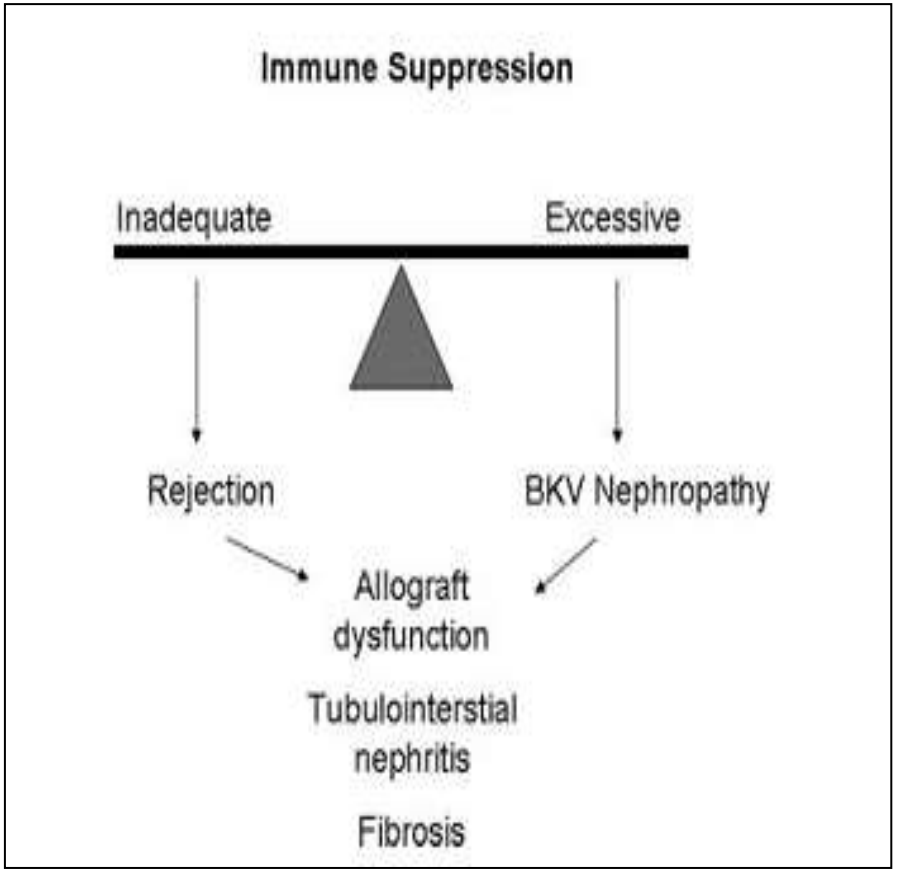
- In addition, patients should undergo PCR-based screening for BKV every time an unexplained rise in serum creatinine occurs, and after treatment for acute rejection.

Treatment of BKVAN

Reduction of immunosuppression

- The most important component of management of BKVAN is a decrease in immunosuppression.
- Most centers withdraw the anti-metabolite and decrease CNI to the lowest possible dose.

Am J Transplant 5: 582–594, 2005



Modification of immunosuppression

Treatment of PVAN by modification of maintenance immunosuppression
Switching
Tacrolimus→CsA (trough levels 100–150 ng/mL) (*B-III*)
MMF→azathioprine (dosing ≤100 mg/d) (*B-III*)
Tacrolimus→sirolimus (trough levels <6 ng/mL) (*C-III*)
MMF→sirolimus (trough levels <6 ng/mL) (*C-III*)
MMF→leflunomide (*C-III*))

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Modification of immunosuppression

Treatment of PVAN by modification of maintenance immunosuppression

Switching	Decreasing
Tacrolimus→CsA (trough levels 100–150 ng/mL) (*B-III*)	Tacrolimus (trough levels <6 ng/mL) (*B-III*)
MMF→azathioprine (dosing ≤100 mg/d) (*B-III*)	MMF dosing ≤1 g/day (*B-III*)
Tacrolimus→sirolimus (trough levels <6 ng/mL) (*C-III*)	CsA (trough levels 100–150 ng/mL) (*B-III*)
MMF→sirolimus (trough levels <6 ng/mL) (*C-III*)	
MMF→leflunomide (*C-III*))	

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Modification of immunosuppression

Treatment of PVAN by modification of maintenance immunosuppression

Switching	Decreasing	Discontinuing
Tacrolimus→CsA (trough levels 100–150 ng/mL) (*B-III*)	Tacrolimus (trough levels <6 ng/mL) (*B-III*)	Tacrolimus or MMF (maintain or switch to dual drug therapy):
MMF→azathioprine (dosing ≤100 mg/d) (*B-III*)	MMF dosing ≤1 g/day (*B-III*)	CsA/prednisone (*B-III*)
Tacrolimus→sirolimus (trough levels <6 ng/mL) (*C-III*)	CsA (trough levels 100–150 ng/mL) (*B-III*)	Tacrolimus/prednisone (*B-III*)
MMF→sirolimus (trough levels <6 ng/mL) (*C-III*)		Sirolimus/prednisone (*C-III*)
MMF→leflunomide (*C-III*))		MMF/prednisone (*C-III*)

Transplantation 2005;79: 1277–1286

Adjunctive therapies

- Cidofovir
- IVIG
- Leflunomide
- Quinolone antibiotics

Retransplantation after BKVAN

- Retransplantation remains a viable option for patients developing graft loss after BKVAN.

- PVAN recurred in 15% of retransplantations compared with 5% of primary transplantations

Transplantation 2005;79: 1277–1286

Take home message

- BKV infection is very common and limits the improvement in transplantation outcomes.

- Screening and early detection of infection is necessary to initiate pre-emptive measures.

- Viruria precedes viremia and nephropathy
  - Urine cytology
  - Urine PCR
- Viremia
  - More specific for nephropathy

Take home message

- Renal biopsy is gold standard
- Suspect BK when rejection does not resolve with usual therapy
- Reduction of immunosuppression remains the only validated measures for treatment.
- This approach is tricky due to the risk of rejection.


Thank You